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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,922	03/30/2005	Sarah S. Bacus	PU4995USw	6645

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

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09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,922	BACUS ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-in-part, 12-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/06,8/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Election filed June 25, 2007 in response to the Office Action of June 6, 2007 is acknowledged and has been entered. Claims 1-26 are pending in the application and Claims 1-in-part, 12-26 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-in-part, 2-11 drawn to a method of assessing whether a subject who presents with an EGFR-expressing solid tumor, which does not express erbB2/expresses erbB2 is likely to exhibit a favorable clinical response to treatment comprising determining the pre-treatment level of pERK and administering an effective amount of a dual EGFR/erbB2 inhibitor and determining the level of pERK after an initial period of treatment wherein a decrease in the pERK level indicates that the subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to no change or an increase in pERK levels.

2. The response to the restriction requirement of June 6, 2007 has been received. Applicant has elected Group 3, Claims 1-in-part, 2-11 for examination. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

3. Upon review and reconsideration and in view of the prior art, the limitation drawn to administering an EGFR inhibitor is rejoined to the instantly examined invention and limitation drawn to expressed HER2 receptor are also rejoined.

4. It is noted that Examiner has established a priority date of March 5, 2003 for the instantly claimed invention because a review of the parent provisional applications reveal support for the claimed invention only in provisional application 60/451,978 filed March 5, 2003, but not in the earlier provisional

applications. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of March 5, 2003 for the instantly claimed application serial number10/529,922, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell et al (Cancer Research, 2001, 61:6500-6510, IDS item).

The claims are drawn to a method to assess whether a subject with an EGFR-expressing solid tumor, is likely to exhibit a favorable clinical response to said treatment, comprising: (a) determining the pre-treatment level of pERK in said tumor; (b) administering a therapeutically effective amount of an EGFR inhibitor, a dual EGFR/erbB2 inhibitor (e) determining the level of pERK in said tumor after an initial period of treatment where a decrease in the pERK level indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change or an increase in pERK levels (claim 1), wherein the initial period of treatment is the time required to achieve a steady-state plasma concentration of said therapeutic compound (claim 2) wherein the pERK levels are assessed by immunohistochemical methods (claim 3), wherein pERK levels are assessed by comparing the distribution of total erk between nucleus and cytoplasmic compartments of the tumor cell (claim 4), wherein the tumor also expresses erbB2 (claim 5), wherein the tumor over-expresses EGFR (claim 6), wherein the tumor is an epithelial tumor (claim 7), wherein the tumor is head and neck tumor (claim 8), wherein therapeutic agent is a dual EGFR/erbB2 inhibitor (claim 9).

Albanell et al teach that their studies in head and neck carcinoma indicate that EGFR blockade inhibits pERK activation and tumor cell proliferation in patients in an EGFR-dependent tissue, wherein specific patient data is disclosed pre and on treatment, (p. 6507, col 2), wherein the EGFR receptor is overexpressed (see Table 2, p. 6503) and specifically state that as a result of the instant studies, assessment of ERK1/2 activation levels in pre- and post-therapy tumor biopsies from patients treated with anti-EGF receptor tyrosine kinase inhibitor ZD1839 (recognized by the art to inhibit both erbB2 and EGFR and thus a dual

EGFR/HER-2 inhibitor) or with MAb C225, an EGFR inhibitor, are added to their protocol (p. 6509, col 1), wherein the reference specifically states that this information will promote a better understanding of EGFR-dependent pathways in vivo and specifically suggests that this information may be of assistance in predicting the subset of EGFR-positive tumors that will benefit from therapy with EGFR inhibitors (p. 6500, col 2), wherein the reference specifically teaches that the pERK levels are assessed immunohistochemically and specifically are assessed by comparing the distribution of total erk between nucleus and cytoplasmic compartments of the tumor cell (p. 6502, col 2), wherein the tumor is an epithelial tumor, wherein the tumor is head and neck carcinoma (6503, col 2) wherein the reference teaches that most of the 101 carcinoma samples assayed were negative for erbB2, but that 19 out of 101 tumors did express erbB2 (p. 6503, col 2) and that dose levels of therapeutic at or greater than 200 mg/m2 achieve sustained, steady state serum concentrations of therapeutic above 200 nmol/liter, a concentration high enough to result in optimal antitumor activity in preclinical models (p. 6507).

Albanell et al teach as set forth above but do not specifically teach a method to assess whether a subject with an EGFR-expressing solid tumor, is likely to exhibit a favorable clinical response to said treatment, comprising: (a) determining the pre-treatment level of pERK in said tumor; (b) administering a therapeutically effective amount of an EGFR inhibitor, (e) determining the level of pERK in said tumor after an initial period of treatment where a decrease in the pERK level indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change or an increase in pERK levels wherein the initial period of treatment is the time required to achieve a steady-state plasma concentration of said therapeutic compound.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Albanell et al to make a method for assessing whether the subject with an EGFR expressing tumor is likely to exhibit a favorable-clinical response to a treatment with an EGFR inhibitor comprising determining the pre-treatment level of pERK in said tumor, administering a therapeutically effective amount of an EGFR inhibitor, determining the level of pERK in said tumor after an initial periods of treatment with said therapeutic agent wherein a decrease in the pERK level indicates that said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change or an increase in pERK levels because Albanell et al specifically suggest making the method for predicting the subset of EGFR-positive tumors that will benefit from therapy with EGFR inhibitors based on analysis of the activation of pERK for head and neck cancers, wherein the reference specifically discloses the reduced activation of pERK in patients treated successfully treated with the EGFR inhibitor compared to control, wherein the reference specifically discloses the reduced activation of pERK in a patient on-protocol compared to the activation of pERK pre-treatment effects of EGFR inhibitor on pERK activation in a patient, wherein the reference specifically states that the assay for pERK activation is being incorporated into current protocols used by the authors of the reference and that the samples used for immunohistochemistry to assess pERK activation are taken from primary tumor, not only pre-treatment but also post-therapy. It would have been prima facie obvious to substitute an on-treatment sample for the post treatment sample of Albanell et al in order to determine whether or not the anti-EGFR treatment was successfully treating the cancer before continuing therapy. Further, it would have

been prima facie obvious to one of ordinary skill in the art, and one would have been motivated to sample the tumor after an initial period when a steady state plasma concentration of the therapeutic compound was in the system to determine the effects of the therapy after a steady state serum concentration of therapeutic known to achieve optimal antitumor activity in preclinical models had been achieved. One would have been motivated to modify the method of Albanell as set forth above because of the clear suggestion of Albanell to make the instantly claimed method and one would have a reasonable expectation of successfully making the method given the clear demonstration of reduction in activated pERK with administration of anti-EGFR inhibitor wherein cellular proliferation associated with said pERK activation was reduced wherein the patients were treated with a therapeutic known to successfully treat head and neck cancer.

Further, the Supreme Court has determined, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S._, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not " be led only to those elements of prior art designed to solve the same problem....." (KSR, 550 U.S. at_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at_, 82 USPQ2d at 1397) and has further determined that

".....[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at_, 82 USPQ2d at 1395). The court further found that "..... the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at_, 82 USPQ2d at 1396).

Given the above, applying the same logic to the instant process claims, it would have been *prima facie* obvious to modify the method of Albanell to produce the instantly claimed method because Albanell specifically recognized the problem or need in the art to solve the problem of identifying the subset of patients that would benefit from EGFR therapy by assaying activated pERK,. Clearly the work was available in this area given the extensive information disclosed by Albanell et al drawn to the nexus between successful anticancer treatment with EGFR inhibitor and reduction in activated pERK,. Further, given the known problem to be solved, given the known conventional and successful techniques for solving the problem, given that Albanell provides a specific identified, predictable, potential solution to the recognized problem, the variation of the technique of Albanell et al to specifically identify those patients likely to benefit from anti EGFR is obvious.

Finally, given the above, the claimed invention is obvious over the prior art because it would have been obvious to try the known methods suggested by Albanell for the identification of that subset of cancer patients that would benefit

from EGFR therapy with a reasonable expectation of success wherein the success of the solution would be a product of ordinary skill and common sense but not the product of innovation.

7. Claims 1 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell et al (Cancer Research, 2001, 61:6500-6510), *Supra* and further in view of US Published Patent Application 20040127470.

The claims are drawn to a method to assess whether the subject with an EGFR expressing solid tumor, is likely to exhibit a favorable clinical response to said treatment, comprising: (a) determining the pre-treatment level of pERK in said tumor; (b) administering a therapeutically effective amount of an EGFR inhibitor, (e)determining the level of pERK in said tumor after an initial period of treatment where a decrease in the pERK level indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change or an increase in pERK levels (claim 1) wherein therapeutic agent is a dual EGFR/erbB2 inhibitor (claim 9) wherein the therapeutic agent is GW572016 (claim 10).

Albanell teaches as set forth above, but do not teach the claimed assessment method with a dual EGFR/erbB2 inhibitor GW572016.

US Published Patent Application 20040127470 specifically teaches that GW572016 is a EGFR antagonist (see claim 13). Examiner takes notice that the art recognized that GW572016 is a dual EGFR/ erbB2 antagonist which would necessarily inhibit both EGFR and erbB2.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute EGFR antagonist GW572016 for any of the EGFR antagonists of Albanell et al in the obvious method as set forth above

in order to determine whether or not the efficacy of this therapeutic can be assessed by this method. One would have been motivated to substitute EGFR antagonist GW572016 for any of the EGFR antagonists of Albanell et al in order to increase the field of knowledge drawn to therapeutics that are more likely to exhibit a favorable clinical response than not.

8. Claims 1 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albanell et al (Cancer Research, 2001, 61:6500-6510), *Supra* in view of US Published Patent Application 20040127470, *Supra* and further in view of Rusnak et al (Cancer Research, 2001, 61:7196-7203) .

The claims are drawn to a method to assess whether a subject with an EGFR expressing solid tumor, is likely to exhibit a favorable clinical response to said treatment, comprising: (a) determining the pre-treatment level of pERK in said tumor; (b) administering a therapeutically effective amount of an EGFR inhibitor, (e)determining the level of pERK in said tumor after an initial period of treatment where a decrease in the pERK level indicates said subject is more likely to exhibit a favorable clinical response to treatment with said therapeutic agent, compared to a subject with no change or an increase in pERK levels (claim 1) wherein therapeutic agent is a dual EGFR/erbB2 inhibitor (claim 9)wherein the therapeutic agent is GW572016 (claim 10), wherein the initial treatment period is from about 14 days to about 28 days (claim 11).

Albanell et al, US Published Patent Application 2004012740 teach as set forth above but do not teach that the initial treatment period is from about 14 to 28 days.

Rusnak et al specifically teach dual EGFR/erbB-2 inhibitors of EGFR catalytic activity with efficacy in inhibition of EGFR overexpressing HN5 head

and neck carcinoma cancer cell growth, wherein the HN5 cells are an established model for EGFR-driven tumor growth, both *in vitro* and *in vivo* (p. 7197, col 1), wherein treatment continued for 21 days (p. 7199, col 1), wherein GW2974 inhibited HN5 tumor growth in a dose dependent manner, wherein the specification teaches that the ability of the dual receptor inhibitors to inhibit the growth of HN5 cells is similar to that of the EGFR tyrosine kinase inhibitor OCI-774 (p. 7201, col 1). The reference further teaches that the EGFR has been shown to transduce a mitogenic signal after autophosphorylation by activating Ras, which then signals through activation of ERK2, resulting in translation of intermediate early response genes and ultimately cell division.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute EGFR/ erbB2 dual inhibitors of Rusnak et al for any of the EGFR antagonists of Albanell et al in the obvious method as set forth above in order to determine whether or not the efficacy of this therapeutic can be assessed by this method. One would have been motivated to substitute EGFR/ erbB2 dual inhibitors of Rusnak et al for any of the EGFR antagonists of Albanell et al because Rusnak et al specifically point to the activation of pERK as a possible mechanism of action of the anti-EGFR therapeutics and further in order to increase the field of knowledge drawn to therapeutics that are more likely to exhibit a favorable clinical response than not. In addition one would have been motivated to substitute the GW572016 of the published application and to assay after a period of 21 days because Rusnak et al make clear that a 21 day period was sufficient to achieve therapeutic efficacy and it would be expected that the therapeutic efficacy would reflect a steady state concentration of drug to effectively treat the head and neck tumor.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 19-24 of copending Application No.10/568,251. Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the copending application and would have been obvious in view of the copending claims which have all of the characteristics of a method of assessing whether a human subject in need of for an EGFR-expressing solid tumor comprising assessing whether the subject is likely to exhibit a favorable clinical response to

said treatment comprising deterring the pre-treatment level of pERK in said tumor which reads on determining that level in various compartments of the cells, administering an EGFR/erbB2 tyrosine kinase inhibitor wherein a change in the distribution of the total pERK between nucleus and cytoplasm, that a decrease in nucleus, compared to the cytoplasm, indicates that the subject is more likely to exhibit a favorable clinical response to treatment.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date as set forth above for the instantly claimed invention, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Ungar
Primary Patent Examiner
August 28, 2007